Karolinska Institutet

Institutionen för Kvinnors och Barns Hälsa

On neonatal asphyxia:

Clinical and animal studies including development of a simple, safe method for therapeutic hypothermia with global applicability

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Leksellsalen, Eugeniahemmet, Karolinska Universitetssjukhuset

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Abstract

Recent randomized clinical trials show that hypothermia can decrease brain dysfunction in newborn infants at risk for hypoxic-ischemic encephalopathy. One goal of the present study was to develop an alternative to current relatively complex and expensive cooling methods dependent on electricity and continuous water supply. An effective and cheap cooling method for global implementation both during transportation and in hospitals based on Phase Changing Material (PCM) was developed. It was found that a specific Glauber salt composition fulfilled safety, cooling and easy of handling criteria and the material was tested in piglets and newborn babies with results comparable to those with conventional cooling. A second goal was to evaluate near red infrared spectroscopy (NIRS) for non-invasive in vivo monitoring of cortical vascular haemodynamic responses to sensory stimuli. NIRS revealed that infants respond more strongly to their mothers' faces than to that of strangers. Preliminary results suggest NIRS may become a useful method for monitoring effects of hypoxic ischemia and its treatment by cooling. When newborn infants at risk are born outside a hospital with cooling facilities, cooling during transport may be beneficial. We found that passive induction of hypothermia during transport is possible, although temperatures of the infants will vary depending on climate and other circumstances, and that such passive measures can lead to unintended excessive cooling necessitating careful monitoring of body temperature. The PCM cooling material was tested as an alternative to water bottle cooling in a piglet hypoxic ischemia model and found to be effective and possibly leading to a more stable target temperature. To better understand how hypoxic ischemia affects different brain areas, brains from piglets subjected to standardized hypoxic ischemia and treatment protocols consisting of cooling, xenon or a combination thereof were analysed with respect to transcriptional activity of key genes, using quantitative in situ hybridization. Analysing mRNA species coding for BDNF, MANF, HSP70, GFAP, NgR, MAP2, LDH-A and LDH-B revealed marked effects of the hypoxic ischemic insult, partial counteraction of mRNA alterations by the treatments and differences between brain areas, as well as possibly between core and mantle regions. In a separate set of animals, different cooling temperatures were compared with respect to the activity of the same set of genes. Cooling to 33°C appeared to be advantageous, while cooling to a rectal temperature of 30°C appeared to be associated with some unwanted effects. It is concluded that cooling can be better controlled and at the same time more easily be made globally available using PCM material, and that cooling partially counteracts some, but not all changes of a selected set of brain mRNA species observed 2-3 days after hypoxic ischemia in a piglet model.

Keywords: PCM, HIE, Hypothermia

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